when in formula (II) W = C, m = 1 and R_0 = -$(CH_2)_n$-NH_2 with n = 1, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = p_2 = p_3 = 0, R_4 = H, R_5 = Q = CH_3, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as pregabaline;

when in formula (II) W = C and has configuration (S), m = 1 and R_0 = -$(CH_2)_n$-NH_2 with n = 1, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = p_2 = p_3 = 0, R_4 = H, R_5 = Q = CH_3, in the radical A of formula (I) T_1 = CO and the free valence of A is saturatd with OH, the precursor drug of R is known as (S)3-isobutylGABA;

when in formula (II) W = C, m = 1 and R_0 = R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q is the guanidine group, in the radical A of formula (I) T_1 = NH and the free valence of A is saturated with H, the precursor drug of R is known as agmatine;

when in formula (II) W = C, m = 2 and R_0 = -$(CH_2)_n$-NH_2 with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = p_2 = p_3 = 0, R_4 and R_5 are free valences and between C_1 and C_2 there is one ethylene unsaturation, Q = H, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as vigabatrine;

when in formula (II) W = C, m = 0 and R_0 = -$(CH_2)_n$-NH_2 with n = 0, R_1 = H, R_2 is the radical 3-4 di-hydroxy substituted benzyl, T_1 = CO and the free valence of A is saturated with OH, the percursor drug of R is known as 2-amino, (3,4-dihydroxyphenyl)propanoic acid (dopa).

Generally the precursor drugs of R are synthesized according to the methods reported in "The Merck Index, 12th Ed." (1996). When the precursor drugs of R comprise in the

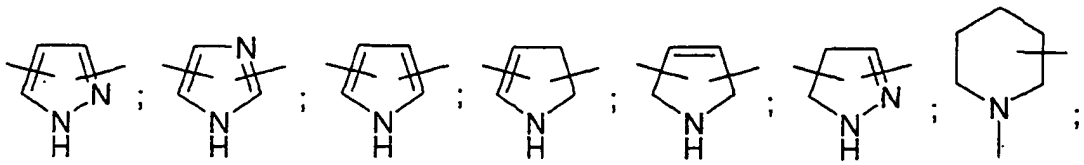
molecule the radical of formula (IIa), they can be synthesized as described in patent application WO 00/79658.

The precursor compounds of B of the above groups are prepared according to the methods known in the prior art and are described, for example, in "The Merck Index, 12th Ed." herein incorporated by reference.

Preferably when in formula (I) b0 = 0, Y in the bivalent linking group C is selected between Y_p and Y_{AR} as above.

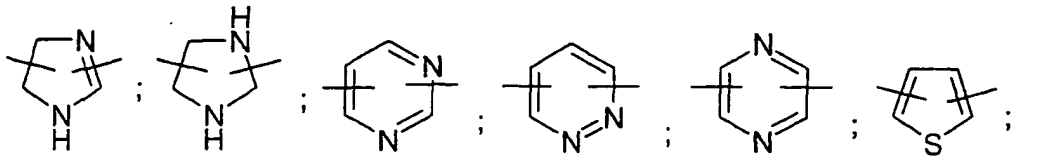
Preferably Y^3 is selected from the following bivalent radicals:

Preferably Y^3 is selected from the following bivalent radicals:

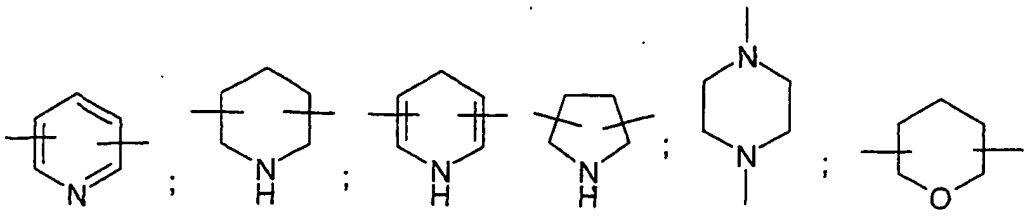


(Y1) (Y2) (Y3) (Y4) (Y5) (Y6)

(Y19)



(Y7) (Y8) (Y9) (Y10) (Y11) (Y18)



(Y12) (Y13) (Y14) (Y15) (Y16) (Y17)

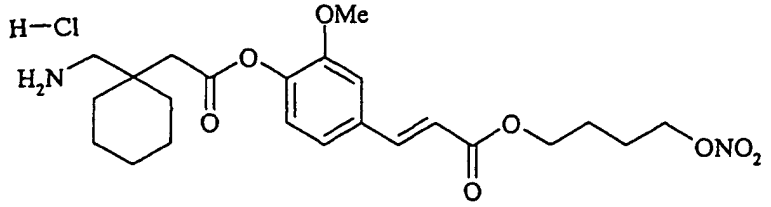
The preferred of Y^3 are the following: (Y12), having the two free valences in the ortho position with respect to the nitrogen atom; (Y16) with the two valences linked to the two heteroatoms, Y1 (pyrazol) 3,5-disubstituted; (Y19), wherein the free valence on the ring is found in para position to the nitrogen atom.

The precursors of Y as defined in formula (III), wherein the free valence of the oxygen is saturated with H and the free valence of the end carbon is saturated either with a caraboxylic or a hydroxyl group, are products available on the market or can be obtained by methods known in the prior art.

In formula (I) the preferred precursors of B for the synthesis of the nitrooxyderivatives usable in the present invention are the following: ferulic acid, N-acetylcysteine, cysteine, caffeic acid, hydrocaffeic and gentisic acid; the preferred precursor drugs are the following: gabapentin, norvaline, arginine, pregabaline, (S)3-isobutylGABA, agmatine.

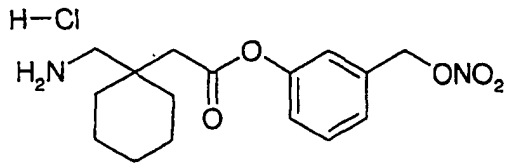
The preferred compounds of formula (I) according to the present invention are the following:

1-(aminomethyl)cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XV)



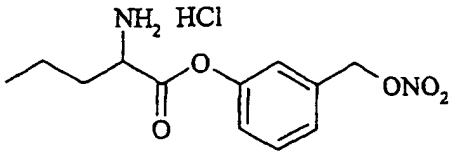
(XV)

1-(aminomethyl)cyclohexan acetic acid 3-(nitrooxymethyl) phenyl hydrochloride ester (XVI)



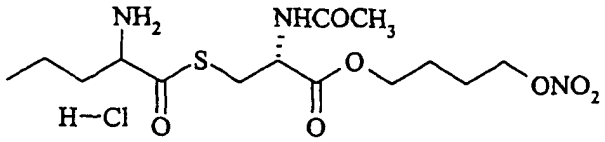
(XVI)

2-aminopentanoic acid 3-(nitrooxymethyl)phenyl hydrochloride ester (XVII)



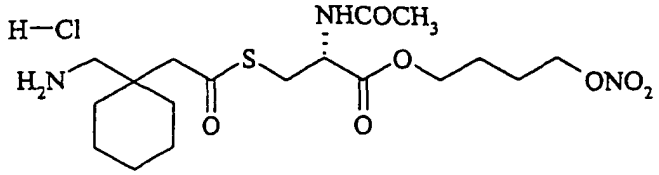
(XVII)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, 2-amino pentanoate hydrochloride (XVIII)



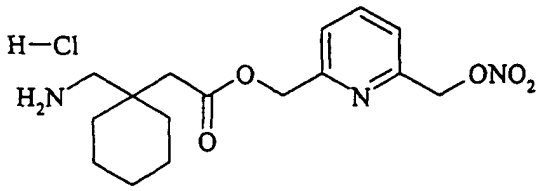
(XVIII)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, 1-(aminomethyl)cyclohexanacetate hydrochloride (XIX)



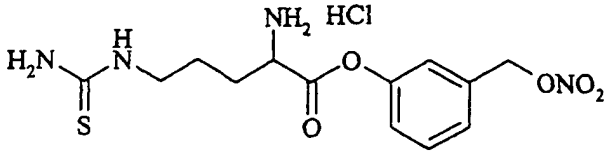
(XIX)

1-(aminomethyl)cyclohexanacetic acid-, [6-(nitrooxy methyl)-2-pyridinyl]methyl hydrochloride ester (XX)



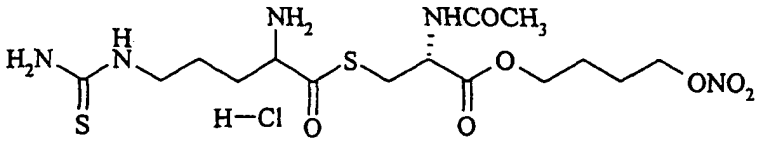
(XX)

alpha-amino-delta-thioureidopentanoic acid, 3-(nitrooxy methyl)phenyl hydrochloride ester (XXI)



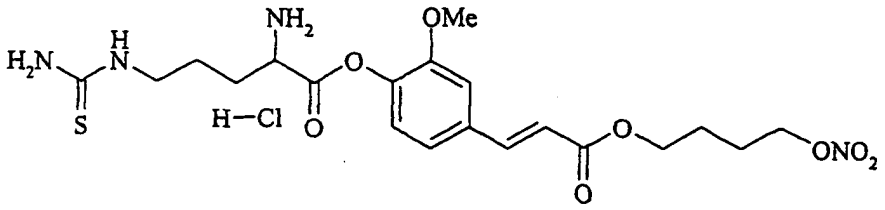
(XXI)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, alpha-amino-delta-thioureidopentanoate hydrochloride (XXII)



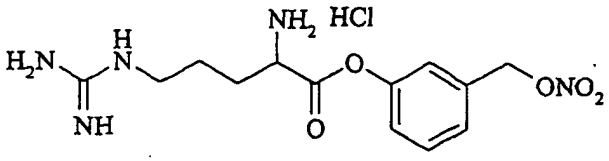
(XXII)

alpha-amino-delta-thioureidopentanoic acid, 2-methoxy-4-[(1E) -3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XXIII)



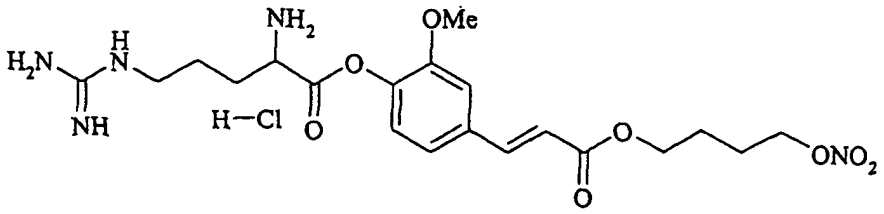
(XXIII)

2-amino-5-guanidinopentanoic acid, 3-(nitrooxy methyl)phenyl hydrochloride ester (XXIV)



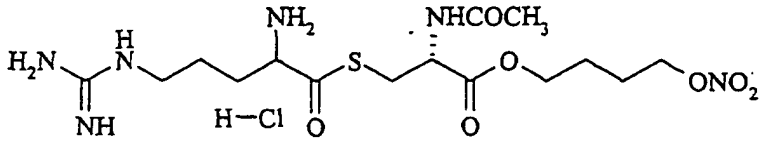
(XXIV)

2-amino-5-guanidinopentanoic acid-, 2-methoxy-4-[(1E)- 3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XXV)



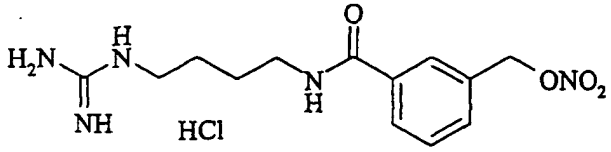
(XXV)

(S)-N-acetylcysteine-4-(nitrooxy)butyl ester, 2-amino-5-guanidinopentanoate hydrochloride (XXVI)



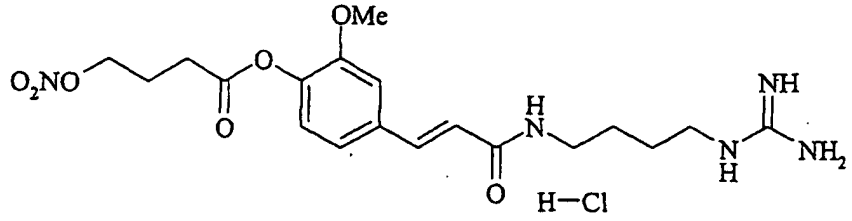
(XXVI)

4-(guanidine)butyl-3-nitrooxymethylbenzamide (XXVII)



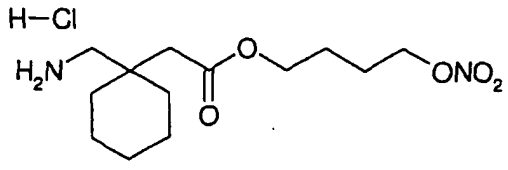
(XXVII)

4-(guanidine)butyl-3-[4-(4'-nitrooxybutyryloxy)-3-(methoxy)]phenyl-2-propenamide chloride (XXVIII)



(XXVIII)

1-(aminomethyl)cyclohexan acetic acid 4-(nitroxy)butyl hydrochloride ester (XXIX)



(XXIX)

The preferred above mentioned compounds with the formulas (XV)- (XXIX) can be used as nitrate salts.

The compounds according to the present invention, when they contain in the molecule one salifiable nitrogen atom, can be transformed into the corresponding salts by reaction in organic solvent such as for example acetonitrile, tetrahydrofuran with an equimolar amount of the corresponding organic or inorganic acid.

Examples of organic acids are: oxalic, tartaric, maleic, succinic, citric acid.

Examples of inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acid.

Salts with nitric acid are preferred.

The compounds of the invention have shown to have an improved activity with respect to the precursor drugs in the epilepsy treatment.

To evaluate the efficacy in the epilepsy treatment of the compounds of the present invention, one of the following pharmacological tests were used.

I) Limbic convulsions induced by pilocarpine (De Sarro G.B. et al. Eur. J. Pharmacol. 349: 179-185, De Sarro G.B., Brain Res. 591: 209-222, Turski W.A., Behav. Brain Res., 9: 315-336).

Male Sprague-Dawley rats weighing 280-350 g were used; they were subcutaneously injected with 1 mg/Kg of scopolamine. 15 minutes later, to the groups of animals the tested nitrooxyderivatives and the corresponding precursor drugs, dissolved in sterile saline solution were respectively administered by intraperitoneal injection. After one hour from the scopolamine injection, pilocarpine hydrochloride,

dissolved in saline solution, was administered by intraperitoneal injection at the doses of 200 or 350 mg/kg.

At the end of the treatments the animals were placed in circular Plexiglass cages (40 cm diameter.) For a time of 180 minutes after the administration of pilocarpine hydrochloride, the onset time and the intensity of the convulsions were checked.

The response of each animal was rated on the basis of a score assigned according to the scheme:

0 no reaction

1 perioral movements and scratching

2 tremors and relaxation of the hind paws

3 head movements and/or animal walking backwards

4 animal rising on the hind paws and tremors of the fore paws

5 falls

6 diffused tremors in the whole body

7 tonic clonic convulsions.

Method by analysis of the electroencephalographic tracing.

In this experiment were used mice belonging to a lethargic mice stock (Lh/Lh) which, when aged of about 15 days develop an ataxic behaviour (Hosford DA Adv Neurol. 1999; 79: 239-252).

The animals, between 11 and 17 weeks old, were anaesthetized with ketamine (7.5 mg/g, i.p.) and medetomidine (0.1 mg/100 g, i.p.). In the frontal cortex and in the parietal cortex (0.8 mm under the dura mater) of each animal two microelectrodes connected to an apparatus for recording the electroencephalographic trace and to a cannula for administering the compounds were inserted.

Once a week, counted by the insertion of the electrodes, an electroencephalographic trace of 2 hours was recorded.

After 15 minutes from the registration of the basic tracing, to the groups of mice solutions of the compounds, the corresponding precursor drugs in sodic phosphate buffer (67 mM) and the carrier were respectively administered by intracerebral infusion (2.5 µl/min for a total volume of 10 µl).

After the pharmacological treatment the electroencephalographic tracing was recorded for 3 hours and the animals were kept under observation for checking behaviour changes.

Absences were quantified on the basis of the duration of the spike discharges on the electroencephalogram as described by Hosford DA et al. Science, 1992 Jul 17; 257(5068): 398-401 (variations of the electroencephalographic trace of amplitudes not lower than 60 µV and of frequencies in the range 5-6 Hz were recorded, attacks must last not less than 0.6 sec).

The electroencephalographic tracing were recorded by amplification of 200-300 µV/cm and with a paper speed of 3 mm/sec.

In order to test the pharmacological effect of the compounds, each electroencephalographic tracing of 3 hours was divided into sections of 30 minutes and for each section the total duration of the spike and wave discharges was calculated; it was then normalized dividing this value by the corresponding value obtained after the administration of the vehicle.

II) Evaluation of anticonvulsant activity in DBA/2 mice after auditory stimulation

Groups of DBA/2 mice (weight 6 to 12 g, 22-26 days old) were treated with testing compounds. All compounds were given intraperitoneally (i.p.) dissolved in sterile saline solution 60 min prior of exposing mice to auditory stimulation. For each dose of compounds studied against audiogenic seizure 10 mice were used.

Each mouse was placed under a hemispheric perspex dome (diameter 58 cm) and left for 1 min in order to allow habituation and assessment of locomotor activity. Auditory stimulation (12-16 kHz, 109 dB) was applied for 1 min or until tonic extension occurred. Seizure response was assessed according to De Sarro GB et al. Neuropharmacology, 23(5):525-30, 1984) using the following scale: 0 = no response, 1 = wild running, 2 = clonus, 3 = tonus, 4 = respiratory arrest. The maximum response was recorded for each animal. Rectal temperature was recorded immediately prior to auditory testing using an Elektrolaboratoriet thermometer type T.E.3. Behavioural changes were monitored during period between drug administration and auditory testing.

III) Evaluation of anticonvulsant activity by convulsant agent pentylenetetrazole

Groups of ICR CD1 mice (weight 16 to 24 g, 42 to 48 days old) were treated with testing compounds to evaluate the pharmacological effects on subconvulsant (40 mg/kg) or convulsant (CD_{97}, 85 mg/kg) dose of pentylenetetrazole was used. All compounds were administered intraperitoneally (i.p.), as above indicated, 60 min before a subcutaneous (s.c.) injection

of pentylenetetrazole (0.1 ml/10 g of body weight). All ICR CD1 mice were observed for 60 min. Animals were scored as seizure positive if they exhibited continuous limb clonus lasting 3 s or of longer duration. For each dose of compounds studied against pentylenetetrazole seizure 10 mice were used.

The compounds of the invention can also be used in combination with NO-donor compounds of the prior art.

The NO donor compounds which can be used in combination with the invention compounds must comply with the test in vitro defined hereinafter.

The test relates to the generation of nitric oxide from the NO donors, for example nitroglycerin, niocorandil, nitroprussiate, etc., in the presence of endothelial cells (method a) or platelets (method b).

a) Endothelial cells

Cells of the human umbilical vein, cultured on plates, having a 10^3 density cells/well were incubated for 5 minutes with scalar concentrations of NO donor (1-100 µg/ml). The incubation medium (physiologic solution, for example Tyrode) was then analyzed to determine the capability to generate NO of the compound under test, by means of:

1) nitric oxide detection by chemiluminescence;
2) cGMP determination (cyclic GMP n° 2715 of the above mentioned Merck).

For the analysis by chemiluminescence, an amount equal to 100 µl was injected in the reaction chamber of a chemiluminescence analyzer containing glacial acetic acid and potassium iodide. The nitrites/nitrates present in the medium, under these conditions, are converted into NO

which is then detected after reaction with ozone, which produces light. In the equipments measuring the chemiluminescence, the produced luminescence is directly proportional to the generated NO levels and can be measured by a suitable photomultiplying unit of a chemiluminescence analyzer. The photomultiplier converts the incident light into electric voltage, which is quantitatively recorded. On the basis of a calibration curve, prepared with scalar nitrite concentrations, it can be quantitatively determined the generated NO concentration. For example, from the incubation of 100 µM of nicorandil, an amount equal to about 10 µM of NO was generated.

For cGMP determination, an aliquot of the incubation medium (equal to 100 µl) was centrifuged at 1,000 revolutions for 20 seconds. The surnatant was removed and the sediment treated with iced phosphate buffer (pH 7.4). The produced cGMP levels were tested by specific immunoenzymatic reactants. From said experiments it resulted that, under these experimental conditions, the incubation with one of the various tested NO donors caused a significant increase of cGMP with respect to the values obtained in absence of a NO donor. For example, after incubation with 100 µM of sodium nitroprussiate, an increase of about 20 times the value obtained with the incubation of the carrier alone, without NO donor was recorded.

b) Platelets

Washed human platelets, prepared substantially in the same way as described by Radomski et al, (Br. J.

Pharmacol. 92, 639-1987), were used. Aliquots of 0.4 ml were incubated for 5 minutes with NO-donor scalar concentrations (1-100 µg/ml). The incubation medium (for ex. Tyrode) was then analyzed to determine the capability of the tested compound to generate NO, by the determination of nitric oxide by chemiluminescence and the determination of cGMP, as described in the previous paragraph for the same analyses carried out on the endothelial cells. For the determination by chemiluminescence, also in this case, on the basis of a calibration curve prepared with scalar concentrations of nitrite, it was possible to quantitatively determine the produced NO amount. For example, after incubation of 100 µM of nicorandil, an amount equal to 35 µM of NO was generated.

For cGMP determination, it resulted that also under these experimental conditions the incubation with one of the tested NO donors gave a significant increase of cGMP with respect to the values obtained in absence of a NO donor. For example, after incubation with 100 µM of sodium nitroprussiate, an increase of about 30 times the value obtaind with the incubation of the only carrier without NO donor took place.

The preferred NO-donor compounds are those which in the molecule contain radicals of drugs belonging to the classes of aspirin, ibuprofen, paracetamol, naproxen, diclofenac, flurbiprofen and are described in patent applications WO 95/20641, WO 97/16405, WO 95/09831, WO 01/12584.

The compounds of the present invention can be synthesized as follows.

Generally when in the drug molecule more reactive groups such as for example COOH and/or HX are present, they must be protected before the reaction according to the methods known in the prior art; for examaple as described in the volume by Th. W. Greene: "Protective groups in organic synthesis", Harward University Press, 1980.

The acylhalides are prepared according to the methods known in the prior art, for example by thionyl or oxalyl chloride, halides of P^{III} or P^{V} in solvents inert under the reaction conditions, such as for example toluene, chloroform, DMF, etc.

1) When in formula (I) b0 = 0 and the free valence of the radical R of the drug is saturated with a carboxylic group, the synthesis methods to obtain the corresponding nitrooxyderivatives are the following:

1.A) The drug of formula RCOOH is treated with an agent activating the carboxyl group selected from N,N'carbonyldiimidazol (CDI), N-hydroxybenzotriazol and dicyclohexylcarbodiimide (DCC) in solvent such as for example DMF, THF, chloroform, etc., at a temperature in the range from -5°C to 50°C and reacted in situ with a compound HO-Y-Hal, wherein Y and Hal are as above defined.

$$RCOOH \xrightarrow{DCC,\ HO\text{-}Y\text{-}Hal} R\text{-}CO\text{-}O\text{-}Y\text{-}Hal \qquad (1C)$$

1.B) Alternatively, the drug acylhalide is reacted with a compound $HO\text{-}Y\text{-}R_{8A}$, wherein Y is as above, R_{8A} is OH or halogen in the presence of a base, in an organic solvent inert under the reaction conditions according to the scheme below reported:

$$RCOHal + HO\text{-}Y\text{-}R_{8A} \dashrightarrow R\text{-}COO\text{-}Y\text{-}R_{8A} \quad (1D)$$

1.C) When the compounds obtained in the above reactions have formula R-COO-Y-Hal the corresponding nitrooxyderivatives are obtained by reacting the compound R-CO-O-Y-Hal with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran according to the scheme:

$$R\text{-}COO\text{-}Y\text{-}Hal + AgNO_3 \longrightarrow R\text{-}COO\text{-}Y\text{-}ONO_2$$

1.D) When the compounds obtained in the above reactions have formula R-COO-Y-OH the hydroxyl group is subjected to halogenation, for example with PBr_3, PCl_5, $SOCl_2$, PPh_3 + I_2, and then reacted with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran.

2) When in formula (I) b0 = 0, and the reactive function of the drug is the group NH_2, the synthesis methods to obtain the corresponding nitrooxyderivatives are the following:

2.a) By reaction of the drug $R\text{-}NH_2$ with an acyl halide of formula Hal-Y-COHal, wherein Y and Hal are as above, according to the scheme:

$$R\text{-}NH_2 + Hal\text{-}Y\text{-}COHal \longrightarrow R\text{-}NHCO\text{-}Y\text{-}Hal \quad (2A)$$

2.b) By reaction of the drug $R\text{-}NH_2$ with an acyl halide of formula OH-Y-COHal, wherein Y and Hal are as above, according to the scheme:

$$R\text{-}NH_2 + Hal\text{-}Y\text{-}COCl \longrightarrow R\text{-}NHCO\text{-}Y\text{-}OH \quad (2B)$$

2.c) When the compounds obtained in the above reactions have formula R-NHCO-Y-Hal or R-NHCO-Y-OH the corresponding nitrooxyderivatives are obtained as above described in 1.C and 1.D respectively.

3. When in formula (I) b0 = c0 = 1, and the free valence of the radical R of the drug is saturated with a carboxylic

group, the synthesis methods to obtain the corresponding nitrooxyderivatives are the following:

3.a) Alternatively the acyl halide of the drug and the compound of formula $HX-X_2-COOH$, wherein X and X_2 are as above, are reacted according to the methods known in the prior art, to give the compound $R-CO-X-X_2-COOH$ which is transformed into the corresponding sodic salt and reacted with a compound of formula $Hal-Y-R_8$ wherein Hal and Y are as above and R_8 is Cl, Br, Iodine, OH:

$$R-COHal + HX-X_2-COOH \dashrightarrow R-CO-X-X_2-COOH \quad (3.A)$$

$$R-CO-X-X_2-COONa + Hal-Y-R_{8A} \dashrightarrow R-CO-X-X_2-CO-Y-R_{8A} \quad (3.A')$$

When R_{8A} = OH the compound of formula (3.A') is subjected to halogenation as above described in 1.D, when R_{8A} = Hal the compound of formula (3.A') is reacted with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran.

3.b) When Y_T is a C_4 linear alkylene, the precursor of B of formula $HO-X_2-COOH$ is reacted with triphenylphosphine in the presence of a halogenating agent such as CBr_4 or N-bromosucciniimide in tetrahydrofuran to give the compound of formula $HO-X_2-COO(CH_2)_4Br$ which is reacted with the molecule of the drug RCOOH as described in 1.A and 1.C.

4) When in formula (I) p = 1 b0 = c0 = 1, and the reactive function of the drug is the group NH_2, the synthesis methods to obtain the corresponding nitrooxyderivatives are the following:

4.a) Reaction of the drug $R-NH_2$ with an acyl halide of formula $HX-X_2-COHal$, wherein X and X_2 are as above, according to the methods known in the prior art, to give the compound $R-NH-CO-X_2-XH$ which is reacted with a compound of formula $R_{8A}-Y-COHal$ wherein R_{8A} and Y are as above.

$R-NH_2 + HX-X_2-COCl \dashrightarrow R-NH-CO-X_2-XH$ (4.A)

$R-NH-CO-X_2-XH + R_{8A}-YCO-Hal \dashrightarrow R-NH-CO-X_2-X-CO-Y-R_{8A}$ (4A')

4.b) Alternatively, the drug $R-NH_2$ is reacted with a compound of formula $HX-X_2-COOH$, wherein X and X_2 are as above, in the presence of dicyclohexylcarbodiimide as described in 1.A, to give the compound $R-NH-CO-X_2-XH$, which is reacted with a compound of formula $R_{8A}-Y-COCl$ wherein R_{8A} and Y are as above defined, to give the following compound: $R-NH-CO-X_2-X-CO-Y-R_{8A}$ (4.B)

When R_{8A} = OH the compound of formula (4.B) or of formula (4a') is subjected to halogenation as above described in 1.D; when R_{8A} = Hal the compound of formula (4.B) is reacted with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran.

When the compounds in the present invention have one or more chiral centres, they can be in racemic form or as mixtures of diastereoisomers, enantiomers, as single enantiomers or single diastereoisomers; when the compound shows a geometric asymmetry the compounds in the cis or trans form can be used.

The compounds of the present invention are formulated in the corresponding pharmaceutical compositions for parenteral, oral use, etc., according to the tchniques well known in the field, together with the usual excipients; see for example the volume "Remington's Pharmaceutical Sciences 15th Ed."

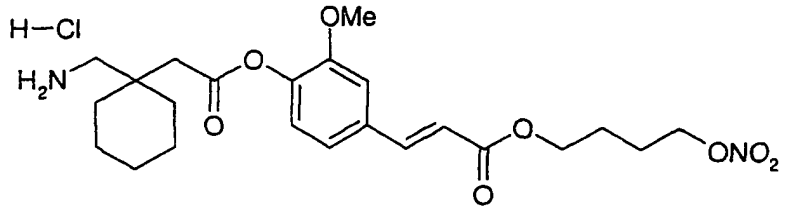
The amount on a molar basis of the active principle in said formulations is equal to or lower than the maximum posology indicated for the precursor drugs. Also higher doses can be used, considering their very good tolerability.

The administrable daily doses are those of the precursor drugs, or even lower. The daily doses can be found in the publications of the field, such as for example in "Physician's Desk reference".

The following Examples illustrate the invention without limiting the scope thereof.

EXAMPLE 1

Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl] phenyl hydrochloride ester (XV)



A) Synthesis of the 1-(N-tert-butoxycarbonylaminomethyl) cyclohexan acetic acid

To a solution of 1-(aminomethyl)cyclohexanacetic acid (10 g, 58.4 mmoles) in a mixture of dioxane (100 ml) and water (150 ml), triethylamine (16.27 ml, 116.8 mmoles) and di-tert-butyldicarbonate (15.3 g, 70 mmoles) are added. The reaction mixture is left at room temperature, under stirring for 4 hours. After having cooled the solution to 0°C it is brought to pH 2 with HCl 5%. The precipitate is filtered and dried under vacuum. 15 g of the expected compound are obtained as a white solid having m.p. = 125°-127°C.

B) Synthesis of 2-methoxy-4-[(1E)-3-[4-(bromo)butoxy]-3-oxy-1-propenyl]phenol

To a solution of ferulic acid (11.6 g, 59.7 mmoles) in tetrahydrofuran (400 ml), tetrabromomethane (39.62 g, 119.47

mmoles) and triphenylphosphine (31.34 g, 119.47 mmoles) are added. The obtained mixture is kept under stirring at room temperature for 5 hours, filtered and evaporated at reduced pressure. The residual crude compound is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 8 g of the expected compound are obtained as a yellow solid having m.p. = 86°-89°C.

C) Syntheis of 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-*propenyl*]*phenol*

To a solution of 2-methoxy-4-[(1E)-3-[4-(bromo) butoxy]-3-oxy-1-propenyl]phenol (8 g, 24.3 mmoles) in acetonitrile (500 ml) silver nitrate (12.25 g, 72.9 mmoles) is added. The reaction mixture is heated at 40°C for 12 hours sheltered from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 75/25. 4 g of the expected compound are obtained as a yellow solid having m.p. = 65°-68°C.

D) Synthesis of the 1-(N-tert-butoxycarbonylaminomethyl) cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl ester

To a solution of 1-(N-tert-butoxycarbonyl aminomethyl) cyclohexan acetic acid (2.5 g, 9.2 mmoles) in chloroform (200 ml) and N,N-dimethylformamide (3 ml), 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl] phenol (3.15 g, 10.1 mmoles), dicyclohexylcarbodiimide (5.7 g, 27.6 mmoles) and N,N-dimethylaminopyridine (33 mg, 0.27 mmoles) are added.

The reaction mixture is left at room temperature, under stirring for 3 hours, filtered and evaporated at reduced pressure. The obtained residue is treated with ethyl acetate

and washed with water. The organic phase is dried with sodium sulphate and evaporated at reduced pressure. The residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 9/1. 5 g of the expected compound are obtained as an oil.

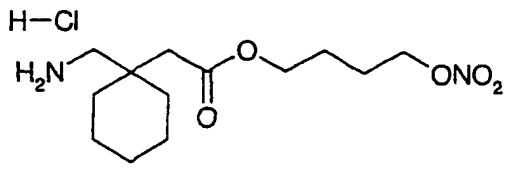
E) Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl] phenyl hydrochloride ester

To a solution of 1-(N-tert-butoxycarbonylamino methyl) cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl]phenyl ester (5 g, 8.8 mmoles) in ethyl acetate (100 ml), a solution of HCl 1N in ethyl acetate (50 ml) is added. The reaction mixture is left overnight at room temperature, then concentrated under vacuum to a volume of 40 ml. The obtained residue is treated with ethyl ether. The precipitate is filtered and dried under vacuum. 1.8 g of the expected compound are obtained as a white solid having m.p. = 103°-105°C.

^{1}H-NMR ($CDCl_3$) ppm: 8.43 (2H, m); 7.55 (1H, d); 7.10 (3H, m); 6.34 (1H, d); 4.51 (2H, t), 4.26 (2H, t); 3.89 (3H, s); 3.12 (2H, s); 2.81 (2H, s); 1.82 (4H, m); 1.54 (10H, m).

EXAMPLE 2

Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 4-(nitrooxy)butyl hydrochloride ester



A) Synthesis of the 1-(N-tert-butoxycarbonylaminomethyl) cyclohexan acetic acid 4-(bromo)butyl ester

To a solution of 1-(N-tert-butoxycarbonyl aminomethyl)cyclohexan acetic acid (1 g, 3.6 mmoles) in N,N-dimethyl formamide (50 ml) cooled at 0°C, sodium ethylate (246 mg, 3.6 mmoles) is added.

The reaction mixture is left at 0°C under stirring for 30 minutes, and then 1,4-dibromobutane (1.28 ml, 10.8 mmoles) is added. The solution is left under stirring at room temperature overnight, then diluted with ethyl ether and washed with water. The organic phase dried with sodium sulphate is evaporated under vacuum. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 0.7 g of the expected compound are obtained as an oil.

B) Synthesis of the 1-(N-tert-butoxycarbonylaminomethyl) cyclohexan acetic acid 4-(nitrooxy)butyl ester

To a solution of 1-(N-tert-butoxycarbonylamino methyl)cyclohexan acetic acid 4-(bromo)butyl ester (1 g, 2.5 mmoles) in acetonitrile (200 ml) silver nitrate (1.3 g, 7.5 mmoles) is added. The reaction mixture is heated at 80°C for 6 hours sheltered from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 0.8 g of the expected compound are obtained as an oil.

C) Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 4-(nitrooxy)butyl hydrochloride ester

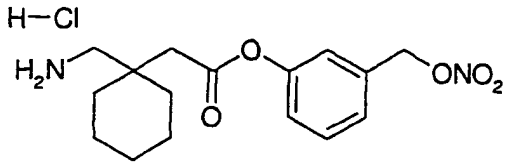
To a solution of 1-(N-tert-butoxycarbonylamino methyl) cyclohexan acetic acid 4-(nitrooxy)butyl ester (0.8 g, 2.06

mmoles) in ethyl acetate (5 ml) a solution of HCl 1N in ethyl acetate (20 ml) is added. The reaction mixture is left for 3 hours at room temperature then it is treated with n-hexane. The precipitate is filtered and dried under vacuum. 0.45 g of the expected compound are obtained as a white solid having m.p. = 80.3°-81.3°C.

^{1}H-NMR (DMSO) ppm: 8.23 (2H, s); 4.58 (2H, t), 4.09 (2H, t); 2.92 (2H, s); 2.56 (2H, s); 1.74 (4H, m); 1.44 (10H, m).

EXAMPLE 3

Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 3-(nitrooxymethyl)phenyl hydrochloride ester (XVI)



A) Synthesis of 3-(bromomethyl)phenol

To a solution of 3-hydroxybenzyl alcohol (4 g, 32.2 mmoles) in methylene chloride (250 ml), cooled at 0°C, tetrabromomethane (12.82 g, 38.6 mmoles) and triphenylphosphine (12.67 g, 48.3 mmoles) are added. The mixture is kept under stirring at 0° for 10 minutes, then evaporated at reduced pressure. The crude product is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 3.5 g of the expected product are obtained.

B) Synthesis of the 1-(N-tert-butoxycarbonylamino-methyl)cyclohexan acetic acid 3-(bromomethyl)phenyl ester

To a solution of 1-(N-tert-butoxycarbonylamino methyl) cyclohexan acetic acid (2.6 g, 9.7 mmoles) in chloroform (200 ml) and N,N-dimethylformamide (2 ml), 4-(bromomethyl)phenol (2g, 10.7 mmoles), dicyclohexylcarbodiimide (4 g, 19.7